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Computational Repositioning of Approved Drug- HCQ for HIV

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ABSTRACT: Repurposing existing drugs presents a promising approach to meeting unmet medical requirements, enabling the creation of new treatments from existing medications that can expedite the development process and reduce expenses. This involves discovering new applications for existing molecules using techniques like ligand- and structure-based methods. HIV causes AIDS, resulting in severe immune system weakening, and despite advancements in treatment, issues like drug resistance continue to exist. The standard treatment for HIV infection is a combination of antiretroviral medications referred to as Antiretroviral therapy (ART). Research into HIV medications has been accelerated by the molecular structure of the gp120 HIV-1, with Hydroxychloroquine being investigated for its various therapeutic impacts, including its anti-malarial properties. The present in-silico repositioning study suggests that HCQ, an anti-malaria drug, may have potential against HIV.However, due to some obvious challenges in repositioning predictions, such as validation consistency, their molecular and physiological effects, further experimental validation is needed for our predictions.

Keywords: Repositioning, HCQ, HIV, 3DNO, Docking.

INTRODUCTION

Drug repositioning/repurposing is used to recognize ingenious strategies for unfulfilled medical needs, which is just the tip of an iceberg (Jourdan *et al.,* 2020). This emerging approach saves time and cost and has vast potential for expediting drug development. Drug repurposing involves exploring new therapeutics for existing molecules to create resourceful therapies out of deserted and existing molecules/drugs (Kharkar *et al.,* 2015). Ligand- and structure-based approaches are well-known to the drug repositioning fraternity (Adasme *et al.,* 2021). Inverse virtual screening using molecular docking (also called reverse docking) represents a structure-based computational strategy wherein a small molecule ligand/drug is screened for its binding complementarity against a clinically relevant database of macromolecular targets (Kharkar *et al.,* 2014; Prada Gori *et al.,* 2023; Sharma *et al.,* 2025; Verma *et al.,* 2024). Computational repositioning, along the expected path, is a systematic method concerned with designing and evaluating automated processes capable of delivering possible new explicit statement hypotheses for a query drug. It depends on the quantity and complexity of clinical or safety data available for the lost, shelved, or activated drugs repurposed, as computational repositioning can further enhance the necessary timeline (Hurle *et al.,* 2013). Some of the significant successes using this approach of repositioning the drug strongly indicate its potential, such as in cardiorenal diseases (Perco *et al.,* 2025), in breast cancer (Jurj *et al.,* 2025), and in Alzheimer's (Hassan *et al.,* 2023). However, a great hope is there for other diseases also, such as Tuberculosis (Doke *et al.,* 2023).

AIDS is caused by HIV infection and is described by a severe decrease in CD4+ + T cells, which indicates that an infected individual builds up a very compromised immune system and becomes susceptible to life-threatening infections (McCune, 2001; Deeks *et al.,* 2013; Deeks *et al.,* 2015). In HIV disease, Human Immunodeficiency Virus types I and II are the causative agents. These two viruses have indeed been described as the primary cause of acquired immunodeficiency syndrome (AIDS) since the initial diagnosis of the Human Immunodeficiency Virus type I (HIV-1) in 1983 and HIV-2 in 1986 (Barré-Sinoussi *et al.,* 1983; Clavel *et al.,* 1986). Given all the clinical advantages gained over the last decade, along with the evolution of "HAART," it is challenging to eliminate the virus once

a person has been diagnosed. However, new concerns are emerging about the short- and long-term exposure to drug therapies and the development of resistance mutations in both active and circulating viruses. In the last couple of years, after pandemics, several attempts have been made to repurpose approved drugs for AIDS and other viral diseases (Ha *et al.*, 2023; Winkler, 2024; Rondina, 2025).

HIV-1 belongs to the lentivirus family and is a retrovirus (Freed & Mouland, 2006). Lentivirus infections regularly exhibit a chronic course, along with a clinical latency period, persistent viral reproduction, and central nervous system complicity. HIV-1 viral particles are enclosed by a lipoprotein membrane and have a diameter of 100 nm (Briggs & Kräusslich, 2011). Every viral particle comprises 72 glycoprotein complexes incorporated into this lipid membrane, each consisting of a gp120 surface glycoprotein trimmer and a gp41 protein spanning the transmembrane. The attachment of gp120 and gp41 is loose and can consequently instinctively shed gp120. Glycoprotein gp120 can indeed be found in serum as well as in HIV-infected patients' lymph tissue (Rychert *et al.*, 2010). Antiretroviral therapy (ART) is used to treat HIV. ART includes taking a combo of HIV medications (the so-called HIV treatment scheme) daily.

The availability of the molecular structure of gp120 HIV-1 (PDB ID: 3DNO) (Liu *et al.*, 2008) (Fig. 1) facilitated speeding up the research and development of the HIV medication. Such studies were highly dependent on the available data and varied concerning the tool/method used for analysis (Singh & Pandey 2017; Singh *et al.*, 2015). Overall, hypotheses for repositioning were developed based on a review of the literature. In this report, Hydroxychloroquine (HCQ) has been used as the ligand for docking studies. This drug has anti-malarial mechanisms and also has a salubrious impact on chronic discoid or systemic erythematosus and acute or chronic rheumatoid arthritis. The specific action mechanism is not conjectured. Hydroxychloroquine sulfate is a colourless crystalline solid, water-soluble, which compound is 2-[[(7-Chloro-4-quinolyamino]pentyl] ethyl amino]ethanolsulfate (1:1). Sulfate hydroxychloroquine tablets contain 200 mg of hydroxychloroquine sulfate, which is equivalent to a base of 155 mg, and is for oral administration (Fan *et al.*, 2015). In recent days, they have gained increased scrutiny for their alleged Efficacy of COVID-19 as an antiviral agent. The drug is out-of-patent, inexpensive, and generally available in high, medium, and low-revenue countries. HCQ is prescribed to victims with autoimmune diseases, has been shown to repress human immunodeficiency virus type 1 replication in vitro in T cells and monocytes by controlling post-transcriptional modification of the virus (Sperber *et al.*, 1995).

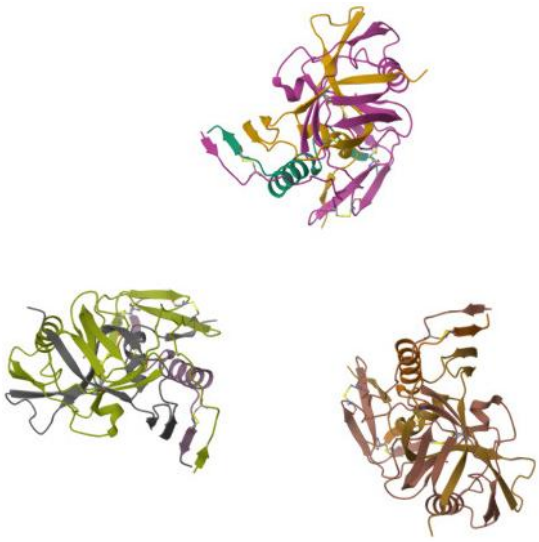

Fig. 1. Molecular architecture of native HIV-1 gp120 trimers (3DNO).

Here, in the present study, an attempt has been made to repurpose hydroxychloroquine, an antimalarial drug also used for treating autoimmune or immune-suppressing diseases one of them is systemic lupus erythematosus (SLE), a rare disease, by molecular docking studies against a molecular envelope protein structure of gp120 timer to comprehend if HCQ can be used for against HIV and to confer if there is any further scope of its study against the same protein.

MATERIALS AND METHODS

Study selection criteria. A thorough literature review was performed on various papers related to HIV, HCQ, and SLE on the basis of which the protein structure and the drug molecule were selected.

Hardware and software. All the computational analyses described here were done on an HP Pavilion Laptop (Intel® Core™ i3, RAM 4 GB) running Windows 10 Home Basic Operating System. Autodock and Autodockdock vina were used for performing various molecular modeling studies. Structure building and related operations were performed using Autodock. The hydrogens were added in the protein, and so were the Kollman charges, which are template values for each amino acid. Preparation of the drug was performed using Pymol and was checked for its stereospecificity, and the output structure was viewed using Discovery Visualization software.

The HIV structure and the molecular structure were studied to find the target-specific site of the protein receptor molecule. A thorough study of HCQ was also performed to understand its structure and its mechanism of action, solubility, and binding. The receptor-ligand interaction was observed, and based on that, various conclusions were drawn

Docking analysis.

Protein structure: The obtained information from the literature review was further subjected to docking analyses in order to study their binding modes (Fig. 2). The starting structure of HIV viral protein 3DNO was obtained from PDB. All Het groups and water molecules were removed from the crystal structure. Polar hydrogen atoms, Kollman–Amber united partial atom charges, and solvation parameters were added by utilizing AutoDockTools-1.5.6.

Ligand structure: The initial structure of 2-[4-[(7-chloroquinolin-4-yl)amino] pentyl-ethylamino]ethanol (Fig. 3) was obtained from PubChem. The top-ranking hits from were imported as .sdf in PyMOL for drug preparation.

Molecular docking: Grid maps of 30 × 30 × 30 points with 0.375 Å spacing generated by AutoGridwerecentered at the ligand-binding site in the crystal structure (Fig. 4). The docking was performed; root mean square tolerance of 1.0 Å. The ligand conformation with the lowest free energy of binding in the most populated cluster was selected for comparison. The results of docking analyses are summarized in Table 1.

RESULT AND DISCUSSION

In the present study, consolidated ligand- and structure-based virtual screening and docking were performed for producing drug repositioning hypotheses for the HIV-1 gp120 trimer in the CD4-bound state, and the location at which the ligand will fit was analysed (Fig. 5A). The binding modes of these potential repositioning candidates were established using molecular docking. The screening/ docking resulted in 9 hits (Fig. 5B), also called poses that show the binding affinity of the ligand; that is, these are the sites amongst which the ligand can bind to the protein (Fig. 5C). More attention was focused on mode 1 out of the nine modes as the first pose showed the best fit from the obtained values, due to the least distance (0.000) with the most concise amount of energy required for the interaction, hence confirming maximum affinity towards the protein (Table 1).

The drug was stereospecific, and the green ball in the ball and stick structure of the drug shows the torsion bond is maximum, and hence the stereospecificity is maximum, and so is the drug interaction at the C8 and N4 positions (Fig. 2), suggesting the best binding possibility at these two sites. The total grid Pts per map obtained were 64000, and the spacing (Å) was 0.375. Therefore, suggesting the possible outcome that the HCQ drug can be used against HIV. The crucial HIV-1 gp120 protein is a potential molecular target against which HCQ therapeutics can be developed; crystal structures and associated ligands were used as a starting point for the combined ligand- and structure-based approaches. The experimental findings would possibly validate the theories and the observations that will enable us to improve anti-HIV medicines.

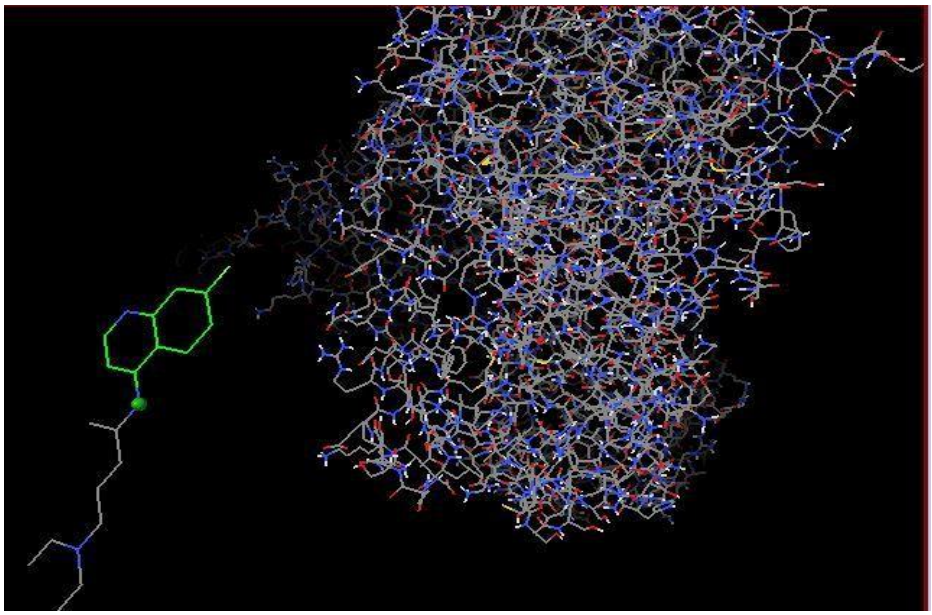

Fig. 2. The stereospecificity of the drug towards the prepared protein in Autodock.

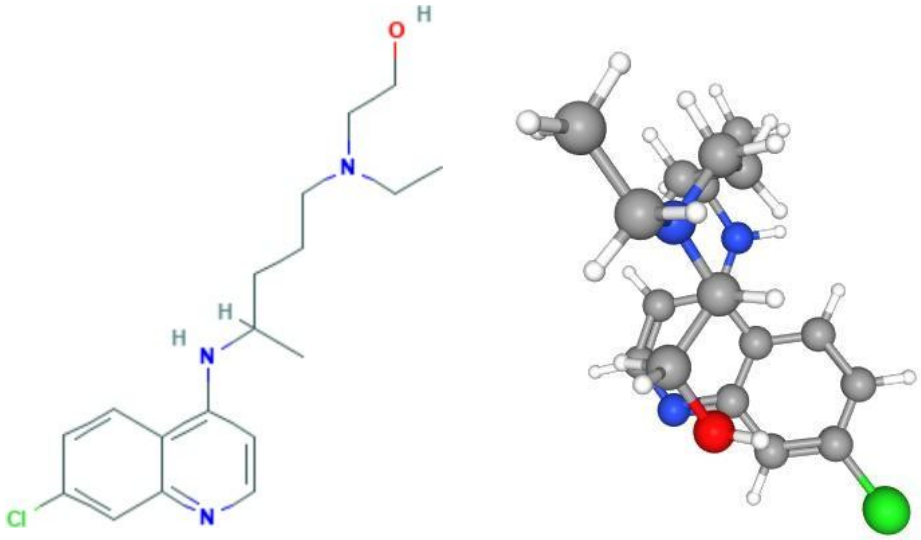

Fig. 3. 3D structure of the drug molecule HCQ

Table 1: Shows the various pose values of nine different poses specifying the energy, distance and the modes.

Mode	Affinity (Kcal/mol)	Dist. (From rmsd)	Best mode (rmsd)
1	-7.3	0	0
2	-7.3	1.5	2.478
3	-6.8	18.685	20.395
4	-6.7	4.532	9.203
5	-6.7	4.018	8.301
6	-6.7	3.886	7.653
7	-6.5	18.693	19.642
8	-6.5	4.305	7.874
9	-6.4	18.485	19.551

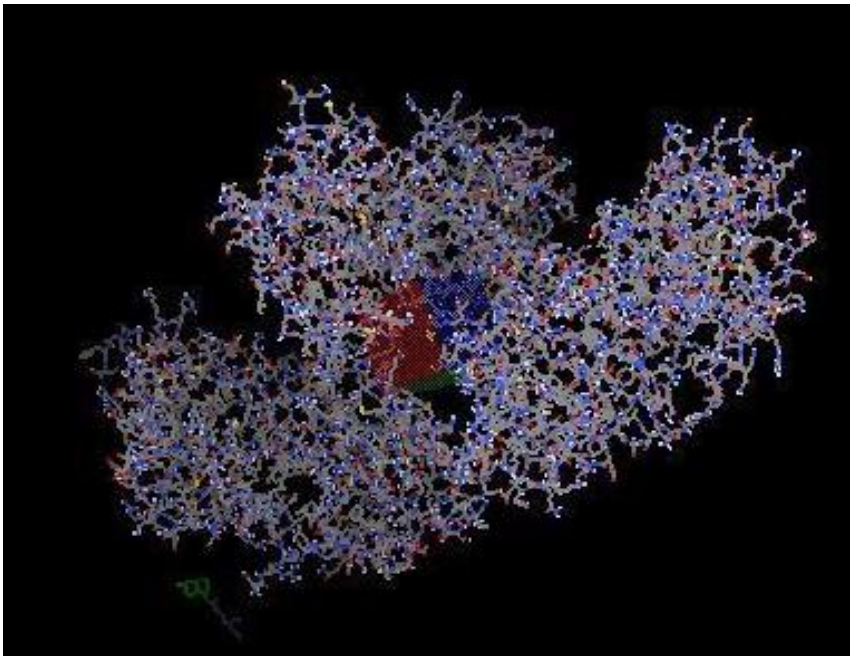

Fig. 4. The docking analysis of the protein and the drug shows the grid box being fit in the centre of the protein structure.

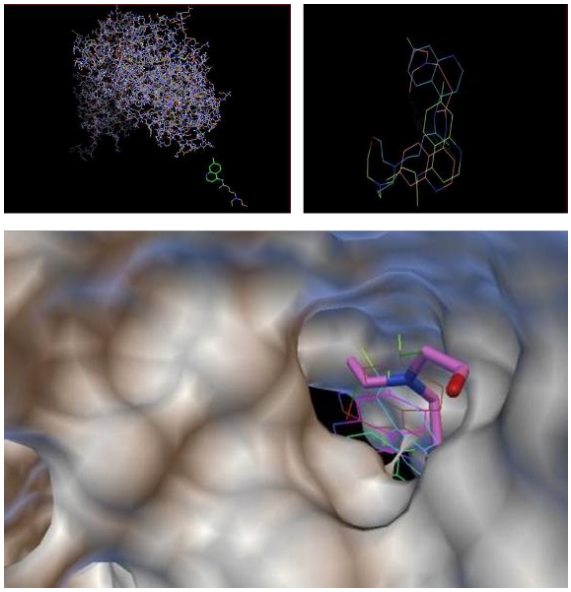

Fig. 5. Shows A.) the site at which the structure will fit best, B.) 9 different ligand sites, C.) the ligand receptor binding

CONCLUSIONS

In the present study, the repositioning hypotheses were generated for approved/existing molecular drugs. The result analysis suggests a possible outcome that the HCQ drug may have a role in against HIV, and future experimental studies can be performed for repositioning of HCQ to be able to come up with an inevitable solution against HIV. However, further experimental validation must also attempt to address the challenges related to repurposing the approved drugs.

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